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PHARMACOGENOMICS-GUIDED PRECISION ANTIMICROBIAL THERAPY: FROM GENETIC VARIABILITY TO PERSONALIZED TREATMENT

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ABSTRACT

Pharmacogenomics (PGx) is a new branch of precision medicine that studies how genetic diversity influences differences in antimicrobial efficacy, drug exposure, toxicity, and treatment response. Although traditional antimicrobial therapy has significantly improved outcomes in infectious diseases, interindividual heterogeneity caused by pharmacokinetic, pharmacodynamic, clinical, pathogen-related, and genetic variables can all contribute to treatment failure or adverse drug reactions. This article outlines the pharmacogenomic foundation of antimicrobial response, which includes genetic diversity in drug-metabolizing enzymes, transporters, immune-related genes, and drug targets. Clinically relevant uses include HLA-B57:01 screening for abacavir hypersensitivity, MT-RNR1-associated aminoglycoside ototoxicity, CYP2B6-related efavirenz exposure, G6PD-associated toxicity, NAT2-related isoniazid metabolism, and CYP2C19-guided voriconazole therapy. The integration of pharmacogenomics with therapeutic drug monitoring, pharmacokinetic/pharmacodynamic modeling, model-informed precision dosing, fast diagnostics, artificial intelligence, and multi-omics may further assist personalized antimicrobial therapy. Pharmacogenomic testing tools ranging from targeted PCR and microarrays to next-generation and whole-genome sequencing open up new avenues for clinical use. India's wide genetic diversity and population-specific pharmacogenomic variations underscore the importance of representative genomic databases, standardized testing panels, clinical recommendations, and outcome-based validation. Despite significant advances, evidence for many antimicrobial gene-drug interactions is still sparse, and implementation is hampered by costs, infrastructure, interpretation, professional education, and unequal population representation. Future research should focus on varied populations, prospective clinical validation, integration with electronic health records, and evidence-based precision antimicrobial management.

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1. INTRODUCTION

Bacterial, viral, fungal, and parasitic infectious illnesses continue to be a major global health concern. Infectious diseases continue to cause significant morbidity and mortality, especially in low- and middle-income countries, despite advancements in antibiotic therapy, vaccination, diagnostics, and public health interventions. Antimicrobial resistance (AMR), which causes treatment failure, extended hospital stays, higher healthcare expenditures, and mortality, further jeopardizes the efficacy of currently available antimicrobial medicines [1-9]. Individual differences in antimicrobial response are significant. Antimicrobial pharmacokinetics, pharmacodynamics, efficacy, and

toxicity can be affected by variations in age, organ function, disease severity, drug interactions, adherence, pathogen susceptibility, and genetic background. An essential method for comprehending and controlling this variability is pharmacogenomics (PGx), which studies how inherited genetic variation influences drug response.

Antimicrobial exposure and treatment outcomes can be affected by genetic variations in drug-metabolizing enzymes, transporters, drug targets, and immune-related pathways. HLA-B*57:01–abacavir hypersensitivity, MT-RNR1–aminoglycoside ototoxicity, CYP2B6–efavirenz exposure, NAT2–isoniazid metabolism, G6PD deficiency–associated toxicity, and CYP2C19–voriconazole variability are examples that are clinically significant. These illustrations show how PGx can be used to support customized antimicrobial selection and dosage and to identify individuals who are more likely to experience treatment failure or adverse medication reactions [10-20].

Integrating genetic testing with therapeutic drug monitoring (TDM), pharmacokinetic/pharmacodynamic (PK/PD) modeling, and model-informed precision dosing (MIPD) can help increase the clinical implementation of antimicrobial PGx. International sites such as CPIC and PharmGKB give evidence and guidance for implementing pharmacogenomic discoveries in clinical practice. However, obstacles such as a lack of clinical evidence, high testing costs, limited infrastructure, complicated variation interpretation, professional knowledge gaps, and population underrepresentation continue to impede wider deployment. Emerging technologies such as quick genetic testing, next-generation sequencing, artificial intelligence (AI), machine learning, and multi-omics techniques may improve antibiotic response prediction and allow for more precise patient-specific therapy. The combination of these approaches with antimicrobial stewardship has the potential to optimize antibiotic use while lowering toxicity and treatment failure [21-30].

India is an important environment for antimicrobial pharmacogenomics due to its high genetic diversity and regional heterogeneity in pharmacogenes. Population-specific genomic initiatives could assist provide information relevant to Indian patients and aid in the development of precision antibacterial treatments [31-34].



Figure 01: From Genes to Personalized Antimicrobial Therapy.

2. THE PHARMACOGENOMIC BASIS OF ANTIMICROBIAL RESPONSE

Pharmacokinetic variability relates to variations in how people absorb, distribute, metabolize, transport, and remove antimicrobial medicines. Genetic differences in drug-metabolizing enzymes and transport proteins can have an impact on drug concentrations, therapeutic results, and toxicity. These distinctions are particularly relevant for medications that require precise therapeutic doses. As a result, combining pharmacogenomic data with pharmacokinetic assessments may aid in optimizing customized antimicrobial treatment [13,14,24,35,36].

Pharmacodynamic variability refers to variances in the biological effects of antimicrobial medicines across individuals. Genetic differences that change medication targets, immunological pathways, and host responses can all have an impact on treatment efficacy and side effects. Single-nucleotide polymorphisms (SNPs) in genes involved in drug metabolism, transport, and immune function can also influence antimicrobial responses. For example, the CYP2B6 516G>T variation has been linked to changed efavirenz concentrations. However, the therapeutic importance of genetic variations varies by drug and community, and many correlations require additional validation. Integrating pharmacogenomic data with PK/PD characteristics andpathogen susceptibility results may enhance response prediction and enable tailored antimicrobial treatment [13,14,18,19,37].

3. HOST GENETIC VARIABILITY IN INFECTIOUS DISEASES

Host genetic differences can affect a person's susceptibility to infections, disease severity, and overall clinical outcome. Variations in genes encoding pathogen identification, immunological signaling, cytokine generation, and host defense may impair the ability to control bacterial, viral, fungal, and parasite infections. Innate immune-response gene variety can alter early defensive systems such as Toll-like receptor activity, interferon signaling, STAT pathways, inflammatory responses, autophagy, and antimicrobial function. Both common genetic variations and rare disease-associated mutations can affect innate immunity, resulting in disparities in infection susceptibility and severity [38-43].

Variations in adaptive immunity genes can influence antigen presentation, T-cell and B-cell activation, antibody generation, and immunological memory. These polymorphisms have been linked to susceptibility and disease development in tuberculosis, HIV, and viral hepatitis. Polymorphisms in cytokine genes, such as IL-6, IL-10, TNF, and interferons, may affect inflammatory responses and influence disease severity and treatment outcomes, albeit more clinical evidence is needed. Variations in the human leukocyte antigen (HLA) impact how pathogen-derived antigens are presented to T cells, influencing immunological detection and

pathogen clearance. Differences in HLA genes have been linked to outcomes in tuberculosis, HIV, hepatitis, COVID-19, and other infections. Understanding these genetic characteristics may improve infection-risk assessment and help develop individualized preventative and treatment measures [44-48].

4. PHARMACOGENOMICS OF ANTIMICROBIAL DRUG METABOLISM

Genetic variations in drug-metabolizing enzymes can influence antimicrobial clearance, drug exposure, therapeutic efficacy, and the risk of side effects. Cytochrome P450 (CYP450) enzymes are involved in the metabolism of several antibacterial and antiviral medicines. Specifically, CYP2B6 genetic variations can affect efavirenz metabolism, potentially increasing medication concentrations and adverse effects.Similarly, mutations in the N-acetyltransferase 2 (NAT2) gene affect isoniazid metabolism, resulting in slow, intermediate, or rapid acetylator phenotypes. These changes may influence medication exposure, therapeutic response, and toxicity, making NAT2 genotyping a promising approach for personalized tuberculosis treatment. UDP-glucuronosyltransferase (UGT) enzymes help with medication glucuronidation and excretion. Although UGT2B7 has been researched in terms of efavirenz metabolism, CYP2B6 appears to have a greater impact on efavirenz concentrations [13,18,19,49,50].

Pharmacogene	Genetic variant	Antimicrobial	Clinical effect
HLA-B	HLA-B*57:01	Abacavir	Severe hypersensitivity reaction; avoid abacavir in positive patients.
CYP2B6	CYP2B6*6 (and other reduced-function variants)	Efavirenz	Increased drug exposure; higher risk of CNS and other adverse effects.
MT-RNR1	m.1555A>G (and other variants)	Aminoglycosides (gentamicin, amikacin, etc.)	Permanent sensorineural hearing loss / ototoxicity.
NAT2	NAT2*5, *6, *7 (slow acetylator variants)	Isoniazid	Altered metabolism and exposure; risk of toxicity or reduced efficacy.
G6PD	Pathogenic G6PD variants	Dapsone	Hemolytic anemia.
G6PD	Pathogenic G6PD variants	Nitrofurantoin	Hemolytic anemia.
G6PD	Pathogenic G6PD variants	Primaquine	Hemolytic anemia.
G6PD	Pathogenic G6PD variants	Nalidixic acid	Hemolytic anemia.
UGT1A1	UGT1A1*28 (and related variants)	Atazanavir	Unconjugated hyperbilirubinemia / jaundice.
HLA-B	HLA-B*57:01	Flucloxacillin	Cholestatic drug-induced liver injury (routine screening not recommended).
HLA-B	HLA-B*13:01	Dapsone	DRESS / hypersensitivity syndrome (consider screening in high-risk populations).

Figure 02: Pharmacogenomic Drug-Gene Interactions.

Drug transporters control the absorption, distribution, cellular uptake, and excretion of antimicrobial drugs. Genetic differences in ATP-binding cassette (ABC) and solute carrier (SLC) transporter genes may affect drug concentrations and treatment responses, albeit their clinical significance varies by drug and community. Genetic polymorphisms in metabolic enzymes and transporters can influence antimicrobial exposure and treatment effects. However, these effects must be weighed against renal and hepatic function, age, illness severity, and drug interactions. Therapeutic drug monitoring (TDM) measures drug concentrations, whereas pharmacogenomics studies genetic variables that influence drug metabolism and transport. Combining these methods with pharmacokinetic/pharmacodynamic (PK/PD) models and individual patient data may assist optimize dose, improve therapy efficacy, and reduce toxicity [14,24-26,35].

5. PHARMACOGENOMICS IN MAJOR INFECTIOUS DISEASES

5.1 Tuberculosis

5.1.1 NAT2 and Isoniazid Metabolism: NAT2 genetic variants alter isoniazid acetylation and define patients as slow, moderate, or rapid acetylators. These variations can affect isoniazid exposure, contributing to heterogeneity in treatment response and side effects. NAT2 thus serves as a key pharmacogenomic marker for personalized tuberculosis treatment [19,49,50].

5.1.2 Genetic Variation and Hepatotoxicity Variations in the NAT2, CYP2E1, and glutathione S-transferase genes have been studied for their relationship with antitubercular drug-induced hepatotoxicity. Slow NAT2 acetylation may increase isoniazid exposure and toxicity risk, however hepatotoxicity is affected by a variety of factors such as age, nutritional st. atus, comorbidities, and concurrent drugs [19,49,51,52].

Infectious Disease	Antimicrobial	Pharmacogenomic Factor	Therapeutic Implication
Tuberculosis	Isoniazid	*NAT2* rapid/slow acetylator status	Dosage adjustment needed for optimal exposure
HIV-1	Abacavir	*HLA*-B*57:01 genotype	Higher risk of hypersensitivity reaction
Malaria (*P. falciparum*)	Tafenoquine	G6PD deficiency status	Contraindicated or use with caution
Hepatitis C (GT1)	Sofosbuvir/Velpatasvir/ Voxilaprevir	G6PD deficiency status	Predictive of response to old treatment (pIFN)
Hepatitis C (GT1) (GT1)	Sofosbuvir/Velpatasvir/ Voxilaprevir	*IL28B* (*IFNL3*) genotype	Predictive of response to old treatment (pIFN)
Hepatitis C (GT1)	Voriconazole	G6PD deficiency status	Dosage adjustment or therapeutic treatment (pIFN) (risk of rcreening n efficacy)
Hepatitis P. (falciparum)	Isoniazid	G6PD deficiency status	Dosage adjustment needed for optimal exposure
Invasive Aspergillosis	Voriconazole	*CYP2C19* metabolizer status	Dosage adjustment or therapeutic drug monitoring
Invasive Aspergillosis	Voriconazole	*CYP2C19* metabolizer status	Dosage adjustment or therapeutic drug monitoring

Figure 03: Pharmacogenomics in Infectious Disease Therapy.

5.1.3 Individualized Antitubercular Treatment: NAT2-guided isoniazid dosing has been studied as a way to maximize medication exposure while minimizing toxicity. According to studies, combining the NAT2 genotype with patient variables such as body weight can improve therapeutic isoniazid concentrations, indicating its potential use in tailored tuberculosis therapy [19,49-52].

5.2 HIV/AIDS:

5.2.1 Genetic Variables Affecting Antiretroviral Response:

Genetic diversity in drug-metabolizing enzymes, transporters, and immune-related pathways can all have an impact on antiretroviral exposure, efficacy, and toxicity. CYP2B6 polymorphisms are especially essential for efavirenz, as reduced-function variations can raise plasma concentrations and lead to side effects. Transporter variations have also been studied, albeit their clinical consequences are inconsistent.

5.2.2 HLA-associated drug hypersensitivity: HLA-B*57:01 screening before to abacavir treatment is a well-established pharmacogenomics application that

significantly lowers the likelihood of abacavir hypersensitivity responses. Other HLA variations have been linked to hypersensitivity to specific antiretroviral drugs, although most have not received the same level of clinical validation [50-53].

5.2.3 Drug Metabolism and Transportation: Antiretroviral medicines are metabolized by CYP enzymes and glucuronidation pathways, and they may also be substrates for membrane transporters. Genetic variations in these pathways can influence medication concentrations and toxicity. One of the more compelling examples is CYP2B6-associated alterations in efavirenz exposure, but evidence for several transporter variants is inconclusive [13,18].

5.3 Malaria:

5.3.1 G6PD and antimalarial Safety: G6PD deficiency is an essential pharmacogenomic issue while taking primaquine and tafenoquine, as these medicines can cause hemolysis in people with low G6PD activity. G6PD variations vary with demographic, especially in malaria-endemic areas. Determining G6PD status before to therapy may therefore increase the safety of these antimalarial drugs [17, 54-57].

5.3.2 Genetic Variability Influences Drug Response:

Genetic variations in drug-metabolizing enzymes may affect antimalarial sensitivity. CYP2D6 variation has been studied in relation to primaquine metabolism since bioactivation contributes to antimalarial activity. However, the link between CYP2D6 genotype, active metabolites, and clinical response is not fully established [15-17,58].

5.4 Viral Hepatitis:

5.4.1 Host Genetic Factors: Genetic variation in the host can influence viral hepatitis susceptibility, illness development, viral clearance, and antiviral therapy response. Variants surrounding the IFNL3/IL28B gene, such as rs12979860 and rs8099917, were significantly related with spontaneous hepatitis C virus clearance and responsiveness to interferon-based therapy.

5.4.2 Antiviral Response Variability IFNL3/IL28B polymorphisms were major predictors of treatment response during the interferon-based treatment era, but their clinical significance has diminished with the widespread use of direct-acting antivirals. Other host variations, such as ITPA and SLC28A3, have been studied for their impact on ribavirin-related toxicity and treatment response [44, 45, 59, 60].

5. 5 Fungal Infections

5.5.1 Genetic variation in antifungal metabolism and response

Genetic differences in drug-metabolizing enzymes and transporters can affect antifungal exposure, efficacy, and toxicity. CYP2C19 polymorphisms have a significant impact on voriconazole metabolism, with poor metabolizers having greater amounts and an increased risk of toxicity. CYP2C19-guided dose in conjunction with therapeutic drug monitoring may thus enable customized voriconazole therapy, although pharmacogenomic evidence for most other antifungal drugs is sparse [13,18].

5.6 Bacterial infections

5.6.1 Genetic Factors Affecting Antimicrobial Exposure and Toxicity:

Host genetic variation can influence antibacterial drug metabolism, exposure, toxicity, and vulnerability to immunological or mitochondrial-mediated adverse responses. MT-RNR1 variations, particularly m.1555A>G and m.1494C>T, are linked to an increased risk of aminoglycoside-induced hearing loss. Thus, avoiding aminoglycosides based on genotype may increase therapy safety in high-risk people. Other drug-gene interactions, such as HLA-mediated hypersensitivity and NAT2-related isoniazid toxicity, highlight the promise of pharmacogenomics for personalized antimicrobial therapy [16, 61-64].

6. PHARMACOGENOMICS-BASED PREDICTION OF ANTIMICROBIAL ADVERSE DRUG REACTIONS

Genetic variants can impact susceptibility to antimicrobial adverse drug reactions (ADRs) via influencing drug metabolism, transport, immunological responses, and physiological pathways. [15-17,19,61]. Variants in NAT2, CYP450, HLA, G6PD, and MT-RNR1 have been linked to a variety of toxicities, including hepatotoxicity, hemolysis, hypersensitivity, and aminoglycoside-induced hearing loss. HLA variants can cause immune-mediated reactions, with HLA-B*57:01-associated abacavir hypersensitivity being a well-documented example; other HLA associations have been studied in reactions to flucloxacillin and cotrimoxazole. G6PD deficiency raises the risk of hemolysis from medications including dapsone, nitrofurantoin, and primaquine, whilst NAT2 slow-acetylator variations may increase isoniazid exposure and hepatotoxicity risk. However, ADR risk is also affected by age, comorbidities, dosage, organ function, and other drugs [15-17,19,53,65-67].

Genetic Variant	Adverse Reaction	Potential Preventive Strategy
*HLA-B**57:01 genotype	Severe hypersensitivity reaction to abacavir	Pre-therapy genotype screening to avoid drug in *HLA-B**57:01-positive patients.
Pathogenic *G6PD* variants (Class I, II, or III)	Hemolytic anemia from dapsone or nitrofurantoin	Pre-therapy *G6PD* testing and selection of alternative agents.
CYP2B6 reduced-function variants (e.g., *6, *18)	Neuropsychiatric adverse events to efavirenz	Consider low-dose efavirenz or an alternative antiretroviral regimen.
NAT2 slow acetylator status	Isoniazid-induced liver injury	Dose reduction or increased frequency of therapeutic drug monitoring.
Pathogenic *G6PD* variants (Class I, II, or III)	Hemolytic anemia from primaquine	Pre-therapy *G6PD* testing; utilize weekly primaquine for Class III.
**UGT1A1 *28* homozygous genotype	Atazanavir-induced hyperbilirubinemia	Use of alternative atazanavir-free regimens or careful monitoring of bilirubin.

Figure 04: Prevention of Genotype-Linked Adverse Reactions.

Pre-treatment pharmacogenomic testing can aid in identifying sensitive patients and facilitating safer antibiotic selection. Examples include HLA-B*57:01 testing before to abacavir therapy, MT-RNR1 testing to determine the risk of aminoglycoside-related ototoxicity, and G6PD testing prior to providing certain medications associated with hemolysis. NAT2 genotyping may also aid in determining susceptibility to isoniazid-induced liver impairment, albeit its clinical use is less established. Because antimicrobial-induced liver injury and other ADRs can be caused by a variety of reasons, genetic findings should supplement, not replace, clinical evaluation, liver function tests, laboratory monitoring, therapeutic medication monitoring, and microbiological data. Routine testing should prioritize clinically proven gene-drug associations, as many hypothesized linkages still require additional proof. [15-17, 53, 62-64, 68, 69].

7. PHARMACOGENOMICS AND ANTIMICROBIAL TREATMENT FAILURE

Antimicrobial therapy outcomes varied amongst individuals due to differences in drug metabolism, transport, renal and hepatic function, body composition, disease severity, infection site, and pathogen susceptibility. Genetic differences in CYP450 enzymes, NAT2, UGTs, and drug transporters can affect drug clearance and exposure. For example, CYP2B6 polymorphisms affect efavirenz metabolism, whereas NAT2 variants effect isoniazid acetylation. Inadequate antimicrobial concentrations may prevent pharmacokinetic/pharmacodynamic (PK/PD) objectives from being met, increasing the likelihood of treatment failure and antimicrobial resistance, while excessive exposure may result in toxicity. When assessing treatment response, host genetics, clinical features, pathogen susceptibility, and minimum inhibitory concentration (MIC) should all be taken into account [13,19,24,35,36,70,71].

Therapeutic drug monitoring (TDM) measures antimicrobial concentrations and guides dose modifications to meet PK/PD targets. Combining TDM with population pharmacokinetic models and Bayesian forecasting enables model-informed precision dosing, which allows treatment to be changed in response to individual drug exposure and changing clinical conditions. Personalized antimicrobial treatment takes into account patient characteristics, pathogen susceptibility,PK/PD targets, and pharmacogenomic information when clinically warranted. These integrated approaches have the potential to improve therapeutic efficacy, reduce drug-related toxicity and unnecessary antimicrobial exposure, lessen the chance of treatment failure, and promote sensible antimicrobial usage [24-26,72-74].

8. PHARMACOGENOMICS AND ANTIMICROBIAL RESISTANCE

Genetic differences can alter antimicrobial drug exposure by changing drug-metabolizing enzymes, including CYP450 enzymes and UGTs, as well as membrane transporters. These variances may influence therapy effectiveness and toxicity, whereas factors such as renal and hepatic function, age, illness severity, and drug interactions all contribute to disparities in drug response. Insufficient antimicrobial exposure may limit the accomplishment of needed pharmacokinetic/pharmacodynamic (PK/PD) parameters and contribute to therapeutic failure, whereas excessive exposure might increase side effects and lead to treatment termination. Therefore, combining pharmacogenomic data with pathogen susceptibility, minimum inhibitory concentration (MIC), therapeutic drug monitoring (TDM), and patient-specific clinical variables can assist identify patients at risk of poor therapy and recommend appropriate therapeutic modifications [6,7,13,24,35,36,70,74].

Pharmacogenomics integrates genetic information with microbiological and clinical data to allow customized antibiotic selection and dose optimization. Important examples include HLA-B*57:01 screening before abacavir therapy to reduce hypersensitivity risk, CYP2C19-guided voriconazole treatment to account for differences in drug metabolism, and MT-RNR1 testing to identify patients at risk of aminoglycoside-associated hearing impairment. In addition, population pharmacokinetic models, Bayesian forecasting, TDM, and model-informed precision dosing (MIPD) can aid in adjusting antimicrobial dosages in response to individual drug exposure and changing clinical conditions. These measures may improve treatment efficacy, reduce toxicity, and encourage proper antibiotic usage. Pharmacogenomic results, however, should be evaluated in conjunction with clinical and microbiological evidence to support safe and successful treatme [15,16,20,25,26,75,76].

9.PRECISION ANTIMICROBIAL THERAPY

Precision antimicrobial therapy uses genetic, clinical, microbiological, and pharmacological data to personalize antibiotic selection and administration.Genotype-guided prescribing can aid in identifying patients who may have changed medication responses or higher toxicity. Important examples include HLA-B*57:01 screening prior to abacavir therapy, MT-RNR1 testing to assess the risk of aminoglycoside-associated ototoxicity, and CYP2C19 genotyping to guide voriconazole therapy. Integrating these genetic discoveries with pathogen identification, susceptibility results, and patient factors could improve therapy safety and efficacy. However, verified gene-drug correlations are scarce, limiting routine pharmacogenomic-guided prescribing to certain therapeutic applications. Individualized dosing is also

required because age, body weight, renal function, disease severity, critical illness, drug interactions, and pathogen susceptibility can all affect antibiotic concentrations. Population pharmacokinetic models, PK/PD targets, Bayesian forecasting, and model-informed precision dosing (MIPD) can help with dose optimization while minimizing toxicity. [15,16,20,24-26,35,75,76].

Application Area	Actionable Variant	Current Status (e.g., guidelines)	Potential Benefit	Emerging Direction	Key Challenge
Cardiovascular	*CYP2C19*2/3*	Guidelines exist for clopidogrel	Prevention of stent thrombosis	Polygenic risk scores (PRS)	Implementation across primary care
Oncology	*UGT1A1 *28*	Guidelines exist for irinotecan	Reducing severe neutropenia risk	Tumor-based vs. germline testing integration	Developing comprehensive tumor-normal panels
Infectious Diseases	*HLA-B*57:01*	Guidelines exist for abacavir	Avoiding severe HSR	Integrating other relevant HLA alleles	Scaling testing cost-effectively
Pain Management	*CYP2D6* poor metabolizers	Guidelines exist for codeine	Preventing overdose risk	Pharmacogenomic-guided opioid-free alternatives	Evidence for specific non-opioid medications
Emerging Applications					
Mental Health	*CYP2D6* and *CYP2C19*	Developing gui-delines for SSRIs	Improving efficacy efficacy	Personalizing dose from pre-genotyping	Establishing standard-of-care implementation
Geriatrics	*CYP3A4/5* variability	Limited guidelines	Optimizing polypharmacy	Predicting whole-drug-load interactions	Large-scale real-world data collection
Immunology	*TPMT* and *NUDT15*	Guidelines exist for thiopurines	Dosage reduction to avoid toxicity	Polygenic contributions to IBD	Finding and validating new targets
Rare Disease	Diverse targets	N/A	Discovering tailored treatments	High-throughput functional genomics	Ethical and cost considerations for N=1 trials

Figure 05: Current vs Emerging Pharmacogenomic Applications.

Therapeutic drug monitoring (TDM) is a key part of precision antimicrobial therapy since it detects drug concentrations and allows for dose adjustments based on individual pharmacokinetic features. It is particularly useful for antimicrobials with narrow therapeutic ranges or significant variability, such as vancomycin and aminoglycosides. It is also being researched for specific β-lactam antibiotics. Combining observed concentrations with population pharmacokinetic models and Bayesian forecasts can aid in ensuring optimal drug exposure as clinical conditions shift. Age, body weight, renal and hepatic function, infection site, disease severity, immunological status, pathogen susceptibility, minimal inhibitory concentration (MIC), previous antibiotic exposure, and relevant genetic information should all be taken into account when making personalized treatment recommendations. Clinical decision-support systems can use these characteristics, as well as drug concentrations and PK/PD targets, to provide personalized recommendations. Artificial intelligence, machine learning, and MIPD platforms may help to improve real-time therapy optimization; nevertheless, successful adoption necessitates verified models, trustworthy clinical data, integration with healthcare systems, and proper professional oversight [24-26, 70, 72-74, 77].

10. ARTIFICIAL INTELLIGENCE AND MACHINE LEARNING IN PHARMACOGENOMICS

Emerging technologies for analyzing pharmacogenomic differences and facilitating individualized antimicrobial treatment include artificial intelligence (AI) and machine learning (ML). In order to categorize genetic variations and evaluate their potential impacts on medication metabolism, treatment efficacy, and toxicity, AI-based methods may analyze complicated genetic information, such as DNA sequence characteristics, evolutionary conservation, and protein-level modifications. ML models are able to predict changes in antimicrobial response and the probability of adverse drug reactions by integrating genetic data with patient characteristics, medication exposure, and clinical outcomes.These technologies may promote optimal drug selection, identify individuals at risk of treatment failure or drug-related problems, and translate genome sequencing results into clinically valuable information. However, model performance, independent clinical validation, diversity of population representation, and the number and quality of datasets all affect prediction accuracy [27-30,78,79].

AI/ML Application	Pharmacogenomic Data Utilized	Actionable Variant	Potential Clinical Benefit
Prediction of Antitubercular Drug-Induced Liver Injury (AT-DILI)	Genotype data, patient demographics, clinical characteristics, and laboratory values.	NAT2, CYP2E1, and other candidate gene polymorphisms.	Enhanced risk stratified screening and early intervention for hepatotoxicity in TB treatment.
Prediction of Abacavir-Induced Hypersensitivity Reaction (AHR)	Whole-genome sequencing and electronic health records.	HLA-B*57:01 genotype.	Precision medicine-based screening and adverse event reduction in HIV treatment.
Prediction of Ribavirin-Induced Hemolytic Anemia	Genotype data, complete blood count (CBC) values, and antiviral treatment response data.	ITPA, SLC28A polymorphisms.	Optimal dose selection and mitigation of adverse anemia in HCV treatment.
Prediction of Voriconazole Pharmacokinetics (PK)	Genotype data, age, weight, and liver function test (LFT) results.	CYP2C19 metabolizer status.	Personalized antifungal dosing and therapeutic monitoring improvement.
Drug-Drug Interaction (DDI) & Pharmacogenomics Prediction	Adverse event reports, genotype data, and electronic health record databases.	Diverse, multi-gene pharmacokinetic and pharmacodynamic profiles	Risk assessment of complex drug regimens and precision dosing in co-infection treatment.
Antiviral Drug Response Prediction	Genotype data, electronic health records, and dynamic physiological signals.	Diverse genetic profiles related to antiviral metabolic pathways.	Optimization of treatment regimens for complex infectious diseases.
Toxicity Risk Prediction for Novel Antiretrovirals	Adverse drug reaction reporting systems and large-scale pharmacogenomic databases.	Rare and novel genetic variants in metabolism and transport genes.	Discovery and development of safer antiretrovirals with predictable safety profiles.

Figure 06: AI Applications in Infectious Disease Pharmacogenomics.

AI and ML may further improve antimicrobial safety by merging genetic information with clinical findings, laboratory results, pharmacokinetic data, and medication-related parameters to evaluate individual toxicity risks. Pharmacogenomic markers can show inherited sensitivity to particular adverse reactions, whereas ML algorithms can combine several risk factors to help doctors identify high-risk patients and propose safer treatment options.Limited population diversity, inconsistent datasets, poor model interpretability, and insufficient external validation continue to be significant obstacles despite these possible advantages. Therefore, before being widely used in clinical settings, AI-assisted pharmacogenomic techniques need to undergo thorough evaluation, transparent models, dependable and representative datasets, and prospective clinical investigations. Their integration into clinical decision-support systems could improve customized antibiotic selection, predict treatment responses, eliminate preventable adverse effects, and advance evidence-based precision medicine [27-30,78-81].

11. MULTI-OMICS IN PRECISION INFECTION MANAGEMENT

Multi-omics technologies combine multiple biological data to increase the understanding, diagnosis, and tailored management of infectious diseases. Genomics reveals genetic variations in the host and pathogens, including characteristics related with illness susceptibility, treatment response, and antibiotic resistance. Transcriptomics studies changes in gene expression during infection, providing insights on

immune responses, microbial activity, inflammation, and disease development. In circumstances such as sepsis, transcriptome analysis may assist detect diverse immune-response patterns and distinguish people who require alternative treatment approaches. [27-30].

Proteomics investigates changes in proteins and their functions, helping uncover potential biomarkers associated to infection, inflammation, tissue damage, disease severity, prognosis, and therapy response. Metabolomics investigates tiny chemicals produced by the host and microbes, showing metabolic alterations related with immunological activation, inflammation, tissue injury, and infection progression. Integrating these four techniques with clinical information can improve biomarker identification, expand understanding of host–pathogen interactions, and promote customized treatment regimens. However, further clinical validation is necessary to verify their reliability and practical application in precision infection treatment. [27-30].

12. PHARMACOGENOMIC TESTING TECHNOLOGIES

Pharmacogenomic testing uses a variety of scientific approaches to uncover genetic variants that influence how people respond to drugs. PCR-based genotyping provides the quick and cost-effective detection of specific, therapeutically relevant variations, making it especially valuable for established drug-gene correlations. However, the discovery of rare, novel, or complicated variations is limited due to its targeted approach.

Microarray-based testing enables the simultaneous investigation of many known genetic variants across multiple pharmacogenes, making it suitable for high-throughput and population-level screening. Nonetheless, it is typically limited to variants represented on the array and may fail to detect uncommon or structural variants [21-23,69,82].

Next-generation sequencing (NGS) expands genomic coverage by allowing the simultaneous investigation of several pharmacogenes and genetic variations. It can detect variants that conventional genotyping may miss, but interpreting rare or complicated variants, sequencing accuracy, and bioinformatic analysis are still significant hurdles. Whole-exome sequencing (WES) investigates the genome's protein-coding regions and may reveal new pharmacogenomic variations not found by targeted techniques [22,23,27,82].

Overall, the choice of pharmacogenomic testing technique is determined by the clinical purpose, needed genomic coverage, cost, and availability of established interpretation methods. When clinically relevant genetic variations are identified, these technologies can enable optimal medication selection and dose optimization, facilitating individualized antimicrobial therapy [23,82,83].

13. INTEGRATION WITH ANTIMICROBIAL STEWARDSHIP

Pharmacogenomics can improve antimicrobial stewardship by enabling tailored antimicrobial selection, dose optimization, and monitoring by combining genetic, clinical, microbiological, and pharmacokinetic data. Validated drug-gene associations may aid in identifying patients at high risk of treatment failure or adverse reactions, whereas therapeutic drug monitoring, PK/PD modeling, Bayesian dosing, and model-informed precision dosing can improve antimicrobial exposure while reducing toxicity and unnecessary drug use. Clinical pharmacists can help with this approach by analyzing pharmacogenomic data, finding drug-gene interactions, adjusting therapy, and monitoring outcomes. The incorporation of pharmacogenomic data into electronic health records and clinical decision-support systems can provide actionable suggestions at the point of prescription, supporting the developing idea of precision stewardship. Validated evidence, standardized interpretation, proper workforce training, digital infrastructure, and equal testing access are all necessary for successful deployment. [23,24,35,72,84].

14. CLINICAL IMPLEMENTATION

Pharmacogenomic testing is especially useful when verified gene-drug connections might help in antibiotic selection, dosage optimization, treatment efficacy, or adverse drug response prevention. Testing can be done before starting a specific medicine or using multigene panels if the results are likely to support future therapeutic decisions. The decision to test should take into account the quality of the available data, prospective clinical advantages, alternative treatment alternatives, testing costs, and result turnaround time. Genetic findings must be interpreted by identifying relevant alleles or diplotypes, estimating expected metabolizer status, and evaluating the strength of the linked gene-drug evidence. Validated clinical guidelines and pharmacogenomic tools can help healthcare providers make effective medication decisions.Genetic findings should be considered with age, renal and liver function, pre-existing medical disorders, concurrent medications, and other pertinent patient features. Pharmacogenomic reports should separate actionable genetic variants from those with limited or uncertain data. They should include the gene, variation, or diplotype, projected phenotype, affected drug, evidence strength, and recommended therapeutic action, if backed by existing recommendations.Standardized reporting enhances uniformity and clarity, while documenting actionable outcomes in electronic health records enables for their use in future prescribing. To ensure successful clinical adoption, pharmacogenomic testing must be integrated into normal procedures such as test ordering, laboratory analysis, interpretation, reporting, treatment decisions, and patient follow-up. When drugs are prescribed,

electronic health records and clinical decision-support systems can provide appropriate suggestions. Professional education, multidisciplinary collaboration, appropriate information technology infrastructure, reimbursement arrangements, institutional protocols, clinician confidence, and adequate training all play a role in wider adoption [21-23,80,82,83,85-87].

15. PHARMACOGENOMICS IN INDIA

India has a high genetic variety due to variances in ancestry, geographical distribution, language groups, and historically distinct people. This diversity can affect the frequency of pharmacogenomic variations, which in turn affects drug metabolism, therapeutic response, and susceptibility to adverse drug reactions. Indian genomic research have revealed population-specific changes in key pharmacogenes, underlining the limits of extrapolating pharmacogenomic data generated mostly from other populations to Indian patients. [31-34].

Large-scale programs, such as IndiGen and GenomeIndia, have improved our understanding of Indian pharmacogenomic diversity. The IndiGen study of 1,029 Indians found potentially important polymorphisms in 102 pharmacogenes, with clinically relevant allele frequencies that differed from worldwide populations. Studies on Indian genomes have also shown population-specific CYP2D6 polymorphisms and changes in projected metabolizer phenotypes, highlighting the potential relevance of Indian-specific pharmacogenomic testing. [32,33,88].

Although pharmacogenomic testing is becoming more widely available in India, its routine clinical application remains limited. High testing costs, limited genetic infrastructure, insufficient population-specific reference data, variant interpretation issues, a lack of standardized testing methodologies, and a lack of knowledge and training among healthcare practitioners are all significant challenges. Developing affordable and standardized Indian-specific pharmacogenomic panels, expanding genomic databases, validating clinically actionable gene-drug associations, and integrating results into electronic health records and clinical decision-support systems could all help with precision antimicrobial therapy in India. India is thus a relevant environment for antimicrobial pharmacogenomics because of its significant genetic variety, which may lead to disparities in antibiotic exposure, efficacy, and toxicity. More population-specific research and prospective clinical validation are required before pharmacogenomic-guided antimicrobial treatment may be applied routinely [23,31-34,82,86,87,89].

16. CURRENT CHALLENGES AND KNOWLEDGE GAPS

Although pharmacogenomics has made significant progress, clinical data for many antimicrobial gene-drug interactions remains insufficient. While some associations, such as HLA-B*57:01 with abacavir hypersensitivity, MT-RNR1 with aminoglycoside-related ototoxicity, and G6PD and NAT2 variants with drug toxicity, have established or promising clinical relevance, many others warrant further investigation and replication in larger studies. The limited representation of diverse ancestral groups in pharmacogenomic research limits the generalizability of findings and the development of inclusive treatment recommendations. Furthermore, simply finding a genetic mutation does not confirm its clinical significance. Functional research, independent replication, consistent interpretation, and accurate conversion of genetic results into clinically significant phenotypes are required, especially for variations with conflicting or insufficient evidence [15-17,19,34,79,81].

Costly testing, insufficient laboratory facilities, payment limits, and limited healthcare resources, particularly in low-income areas, all make practical application difficult. Differences in testing techniques, reporting procedures, clinical protocols, electronic health record systems, and clinical decision-support technologies can result in inconsistent implementation; thus, standardized methods and evidence-based guidelines are required. Inadequate knowledge and confidence among healthcare professionals in test selection, result interpretation, and clinical application also impedes adoption, underlining the importance of ongoing education and specialized training. Furthermore, well-designed, sufficiently powered prospective clinical trials are needed to demonstrate the efficacy of genotype-guided antimicrobial treatment, evaluate its therapeutic usefulness and cost-effectiveness, and determine whether it improves patient outcomes. [23,31,77,82,86,87,90].

17. FUTURE PERSPECTIVES

AI and machine learning (ML) are predicted to promote precision antimicrobial therapy by combining clinical, microbiological, genetic, pharmacological, and antimicrobial-resistance data to aid in personalized drug selection. These technologies may enhance resistance prediction, optimize treatment decisions, and detect treatment failure early on, eliminating unnecessary antimicrobial exposure. Furthermore, quick point-of-care pharmacogenomic testing may reveal clinically relevant genetic variants prior to or during therapy, allowing clinicians to select safer and more effective medications and doses. Improvements in genotyping and sequencing technology, together with lower testing prices, may make near-real-time genetic information more available for tailored antibiotic prescribing. [27,28,30,77,79].

Future research should concentrate on integrating host and pathogen genetic data to better infection control. Host genetic variants affect infection susceptibility, immunological responses, drug metabolism, and the possibility of adverse reactions, whereas pathogen genomic data can reveal resistance determinants, virulence factors, and transmission patterns. Combining these data sets may provide a more comprehensive

foundation for selecting suitable antimicrobial therapy. To enable accurate and practical clinical application, AI-based methodologies and integrated genomic strategies must be implemented successfully. This includes high-quality datasets, thorough clinical validation, interpretable models, and effective integration into healthcare workflows. [27-30,38,42,48].

18. CONCLUSION

Pharmacogenomics is a critical foundation for moving antimicrobial therapy away from traditional population-based treatment and toward tailored precision medicine. Genetic variation can have an impact on antimicrobial metabolism, exposure, toxicity, immune-mediated reactions, and treatment response, and when combined with pathogen susceptibility, PK/PD assessment, therapeutic drug monitoring, and patient-specific characteristics, treatment can be optimized. Established applications, such as HLA-B*57:01-guided abacavir treatment, have demonstrable therapeutic utility, but many more antimicrobial gene-drug correlations require further validation. India presents a significant opportunity due to its vast genetic variety and rising genomic resources, but population-specific databases, standardized testing, clinical recommendations, skilled healthcare workers, and inexpensive access are still required. Future integration of pharmacogenomics with quick diagnostics, multi-omics, artificial intelligence, and electronic clinical decision support may improve precision antimicrobial therapy and stewardship. [30,75,79,91].

19. AUTHOR CONTRIBUTION

All Authors are contributed equally

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21. CONFLICT OF INTEREST

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23. INFORM CONSENT AND ETHICAL STATEMENT

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24. References

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